Relationships Between Thyroid Hormones and Symptoms in Combat-Related Posttraumatic Stress Disorder

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This study was designed to investigate relationships between serum thyroid hormone levels and the severity of posttraumatic stress disorder (PTSD) symptoms in a group of 65 male Vietnam combat veterans who participated as members of cohorts in an elective inpatient treatment program. Thyroid hormone measures included serum free and total triiodothyronine (T3), free and total thyroxine (T4), and thyroxine-binding globulin. To estimate symptom severity, the Clinician-Administered PTSD Scale (CAPS-2), based on DSM-III-R diagnostic criteria for PTSD, was used. Significant positive correlations were observed between free T3, total T3, total T4, and the "hyperarousal" frequency subscale score and the CAPS-2 frequency sum score. Patients with increased thyroid hormone levels and increased hyperarousal symptoms might constitute a clinically significant subtype among patients with PTSD. Alternatively, increased thyroid activity and hyperarousal symptoms may be associated with phase-related characteristics in PTSD. Research strategies for further evaluation of these preliminary findings are discussed.

Key words: thyroid, triiodothyronine, PTSD, stress, hyperarousal.

INTRODUCTION

Among the multidimensional hormonal alterations reported in posttraumatic stress disorder (PTSD) involving the cortisol, norepinephrine, epinephrine, testosterone, and thyroid systems (1), an unusual thyroid hormonal profile is emerging as one of the most striking and potentially significant features (2). The connection between traumatic stress and thyroid function has a venerable history in the psychoendocrine literature, beginning with Caleb Parry's (3) original report in 1825 of the onset of hyperthyroidism in a woman after a terrifying experience in a runaway wheelchair. In 1927, Bram (4) reported a clear history of traumatic stress, such as combat exposure, fires, earthquakes, shipwrecks, and narrow escapes from accidents, in 85% of more than 3000 cases of thyrotoxicosis. Many basic and clinical psychoendocrine studies have since established a strong basis for considering thyroid hormones as "stress hormones," which probably have a clinically significant role in a variety of psychiatric disorders (5–7).

Although it may not be surprising to find thyroid alterations in PTSD, by definition a stress-related disorder involving the persistent reexperiencing of traumatic stress, the nature of the changes in PTSD are apparently not simply those of classic hyperthyroidism but involve a more subtle type of moderate hyperactivity featuring elevations in levels of both free and total triiodothyronine (T3) and total thyroxine (T4) but *no increase* in levels of free T4 (2). The increased thyroid binding measured by elevated levels of thyroxine-binding globulin (TBG) found in patients with PTSD (2) provides one explanation for increased total T4 and total T3. However, the finding that levels of free T3 are elevated and those of free T4 are normal indicates that there must be another mechanism responsible for the sustained thyroid elevations observed in these patients. The resultant increase in the total T3/free T4 ratio suggests the possibility that, in PTSD, there may be an increase in the conversion of T4 into T3, the peripheral enzymatic process that is responsible for about 80% of the total T3 production in the body. The rate of this conversion process appears to be increased by elevated peripheral catecholamine levels, a condition known to be sustained in many patients with PTSD (2).

Given the significantly elevated serum total T4 and total and free T3 levels observed in patients with

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combat-related PTSD compared with those in healthy controls (2), it would be reasonable to suspect alterations in serum thyroid-stimulating hormone (TSH) levels. No significant difference was found between TSH levels in patients with PTSD and healthy controls (2), which supports the notion of increased *peripheral* production of T3 from free T4 as the probable cause of elevated T3 levels observed in these patients. TSH regulation is a complicated biological issue (2); clearly, further study is required to determine what mechanisms, such as negative feedback from T3 or hypothalamic resistance to thyroid hormone, are responsible for TSH findings in PTSD.

Because T3 is metabolically several times more potent than T4 and 64% of a large sample of patients with PTSD were found to have total T3 levels above the upper limit of the range in a normal control group (2), it appears important to explore the possibility that T3 elevations may have a significant clinical role in PTSD. Many of the symptoms of classic hyperthyroidism, such as sleep disturbances, restlessness, anxiety, increased startle, irritability, explosive anger, and difficulty in concentrating (8), are prominent features of the clinical picture in PTSD. As a beginning step in this direction, the purpose of the present article is to examine the relationship between thyroid hormone levels and the frequency of PTSD symptoms, as measured by the Clinician Administered PTSD Scale (CAPS-2), and other clinical measures in combat-related PTSD.

METHODS

The study sample consisted of 65 male Vietnam combat veterans who were recruited for participation as members of 12-patient cohorts in an elective, research-oriented inpatient treatment program of 4 months duration at the West Haven VA Medical Center. This sample was a subset of a larger multisite PTSD sample for which serum thyroid measurements have previously been reported (2). None of the patients was admitted in an acute crisis stage, and all were required to be free of medication during the initial month. The diagnosis of PTSD was established using DSM III-R criteria on the basis of the Structured Clinical Interview for DSM-IIIR (9) and the Mississippi Scale for Combat-Related PTSD (10) with 107 as a cutoff score. Exclusion criteria included major medical illnesses, hormonal medication, organic brain syndrome, and current drug or alcohol abuse. After obtaining informed consent, clinical and hormonal assessments were made concurrently on each patient during a period after hospital admission but before the onset of the treatment program involving an intensive schedule of 32 hours per week of individual and group therapy.

Blood samples and CAPS-2 measurements (11) were obtained on all 65 patients during the admission period. The CAPS-2 measures current PTSD symptoms rather than lifetime symptoms (CAPS-1 version). Other clinical measures included the Mississippi PTSD Scale for Combat-Related PTSD (10), the Combat Exposure Scale (CES) (12), the Impact of Events Scale (IES-intensity) (13), the Brief Psychiatric Rating Scale (BPRS) (14), and the Hamilton Depression Scale (HDS) (15). The Mississippi Scale, the IES, and the CAPS are instruments that were developed specifically for assessment of PTSD symptoms. The Mississippi Scale is a 35-item self-report questionnaire that is used as a general indicator of severity of PTSD. The IES is a 14-item scale that assesses intrusive and avoidant symptoms separately. In this study, it was administered as a self-report instrument. The CAPS-2 is a clinician-administered instrument and measures the frequency and intensity of the 17 PTSD symptoms identified in DSM-III-R and eight items labeled as "hypothesized or associated features." The CAPS-2 frequency score is based on the frequency of occurrence of PTSD symptoms during the past week. A sample question is, "In the past week, have you had unpleasant dreams about the traumatic event? How often?" The response is rated as follows: 0 = never, 1 = once, 2 = two or three times, 3 = four or five times, and 4 = nightly or almost every night. The CAPS-2 intensity score is based on a rating of the most intense PTSD symptoms during the past week. For example, "At their worst, how much distress or discomfort did these dreams cause you?" with 0 = none; 1 = mild, minimal distress; 2 = moderate, awoke in distress but readily returned to sleep; 3 = severe, considerable distress, difficulty returning to sleep; and 4 = extreme, overwhelming or incapacitating distress, could not return to sleep. Subscales of the CAPS-2 include Re-Experiencing (CAPS-B), Avoidance (CAPS-C), and Hyperarousal (CAPS-D). The BPRS is a clinician-administered scale used to assess a broad range of psychopathology. The HDS is a clinician-administered scale that measures depressive symptoms.

The mean values that characterized the patient sample from a demographic and clinical standpoint were as follows: age = 42.7 ± 2.5 years, weight = 85 ± 15 kg, height = 177 ± 6 cm, CES = 30.5 ± 7.8, Mississippi = 132.6 ± 15.2, CAPS-2 sum = 44.8 ± 10.3, IES = 54.2 ± 16.7, BPRS sum = 20.8 ± 9.4, and HDS sum = 17.2 ± 6.7.

Blood samples (10 ml) were collected at 8 to 9 AM, and the serum was divided into three 1.5-ml aliquots and frozen at −70°C until analyzed. Serum total T4 (TT4), free T4 (FT4), and total T3 (TT3) concentrations were measured by radioimmunoassay (RIA) procedures, using kits from the Incstar (Stillwater, MN). The interassay coefficient of variation in our laboratory was 3.7% for TT4, 4.2% for FT4, and 6.0% for TT3. Serum free T3 (FT3) levels were measured by an RIA procedure prepared by Diagnostic Products (Los Angeles). The interassay coefficient of variation for FT3 was 2.7% in our laboratory. Serum TBG concentrations were measured by an RIA procedure prepared by Incstar, and the interassay coefficient of variation was 3.0% for TBG in our laboratory.

RESULTS

Table 1 presents a summary of the Pearson product-moment correlations between thyroid hormone measures and CAPS-2 measures of PTSD symptoms. The CAPS-2 measurements were selectively related to three thyroid measures: TT3, FT3, and TT4. All three of these measures were positively correlated with the CAPS-2 sum and the CAPS-D subscale score for "hyperarousal" symptoms. For both TT3 and FT3, the strongest correlations were with the hyper-

TABLE 1. Correlations Between Hormonal and PTSD-Symptom Measures (N = 65)

		CAPS SUM[a]	CAPS B[b]	CAPS C[c]	CAPS D[d]
Total T3	r=	.376	.192	.291	.407
	p<	**.002****	.12	**.02***	**.0008*****
Free T3	r=	.309	.282	.154	.352
	p<	**.01****	**.03***	.21	**.004****
Total T4	r=	.363	.259	.306	.323
	p<	**.003****	**.04***	**.01****	**.009****
Free T4	r=	.131	.141	.024	.200
	p<	.3	.26	.8	.11
TBG	r=	.191	.156	.130	.179
	p<	.13	.2	.3	.15

[a] CAPS SUM = "B" + "C" + "D" frequency scores.
[b] CAPS B = "Re-experiencing" frequency score.
[c] CAPS C = "Avoidance" frequency score.
[d] CAPS D = "Hyperarousal" frequency score.
*=p<.05, **=p<.01, ***p<.001

arousal measure (r = .407, p < .0008 and r = .352, p < 0.004, respectively). With regard to the three subscales, TT4 also correlated most highly with the hyperarousal score (r = .323, p < .009). As expected, FT4, which is not elevated in PTSD, did not correlate significantly with any of the CAPS-2 measures.

The possibility of some degree of specificity in the relationships between the thyroid system and CAPS-2 PTSD symptoms was supported by the finding that no significant correlations were observed between TT3, FT3, or TT4 and the scores from any of the other clinical rating scales, including the Mississippi Scale, the IES, the BPRS, or the HDS, which provide measures of the severity of a broad range of other clinical symptoms as well as core PTSD symptoms.

The validity of the relationship between TT3 and hyperarousal measured by the CAPS-2 was further supported by its significance (p < .05), after correction for family-wise error, which takes into account the total number of correlations in the study, using a conservative criteria for statistical significance based on the Bonferroni F statistic (16).

Only frequency measures are considered in Table 1 because they were more reliably related to hormones than intensity measures. For example, in the case of the correlation between TT3 and hyperarousal symptoms (CAPS-D), frequency measures showed a much stronger association than intensity measures (r = .407, p = .0008 versus r = .146, p = .15). Similar comparisons were observed with FT3 and TT4.

An alternative method of analyzing the data supports the validity of these findings in our patient sample. With a median split with the CAPS-2 sum scores (cutoff score = 44), comparison by t test of the top half, or "*high* PTSD symptom subgroup" (N = 33), versus the bottom half, or "*low* PTSD symptom subgroup" (N = 32), showed no significant difference between the two subgroups in FT4 levels, but the high PTSD symptom subgroup showed significantly higher levels of TT3 (mean ± standard deviation: 193 ± 44 ng/dl versus 163 ± 27 ng/dl, p < .002), of FT3 (3.4 ± 0.77 ng/dl versus 3.0 ± 0.36 ng/dl, p < .004), and of TT4 (9.1 ± 1.9 μg/dl versus 7.8 ± 1.4 μg/dl, p < .002).

Analysis of the subsample of 35 patients on whom both admission and discharge data were available emphasized the strength of the total T3 relationship with the hyperarousal measure because there were significant positive correlations between these two measures in the admission period (r = .484, p < .009), in the discharge period (r = .460, p < .006), and for the mean values covering all 70 samples (r = .452, p < .006).

DISCUSSION

The principal finding in this study was the discovery of a relatively strong and selective positive relationship between the levels of TT3, FT3, and TT4 and the frequency of PTSD symptoms, especially hyperarousal symptoms, as measured by the CAPS-2 instrument. The six items that make up the hyperarousal scale relate to sleep difficulties, irritability and anger outbursts, difficulty concentrating, hypervigilance, increased startle, and physiologic reactivity. Although the findings with this hyperarousal symptom cluster appear to provide some support for the conclusion that the levels of symptoms commonly associated with clinical hyperthyroidism do correlate positively and selectively with thyroid levels in PTSD, there is a need to zero in on these and other hyperthyroid-linked symptoms with a battery of more specific and custom-tailored instruments for measuring these variables, especially sleep disturbances and increased startle where objective physiological measures can also be included. In addition, the possibility that chronic anxiety symptoms, which can include hyperarousal symptoms, may relate to thyroid measures needs to be more fully explored.

What is the clinical significance of the relationship between hyperarousal and thyroid measures? One possibility is that patients who exhibit elevated thyroid hormone levels and more frequent hyperarousal symptoms may represent a subgroup among patients with combat-related PTSD. If such a subtype exists, then identification of these patients could

have treatment implications. For example, effective pharmacotherapy for the treatment of patients with PTSD has been problematic (17), indicating the need to develop new strategies for medication selection. Medications such as lithium or propranolol, which can lower levels of thyroid hormones, might be chosen over other medications on the basis of a patient being classified in a high thyroid group. Perhaps a portion of the clinical improvement reported among patients with PTSD who received propranolol (18, 19) is related to its effect of reducing the conversion of T4 to T3 decreasing the circulating level of the more biologically active T3. Medication trials that include systematic assessment of thyroid function (both T4 and T3) are needed to determine the relevance of the thyroid profile to clinical improvement in response to particular medications.

Behavioral interventions in patients with PTSD such as imaginal flooding have yielded mixed results (17). It is possible that these techniques are more or less effective with patients in a high-thyroid/hyperarousal subgroup. Given the inconsistent outcomes of medication trials and behavioral interventions with patients with PTSD, the possibility of identifying a biologically distinct subtype among such patients is a promising new development that could help guide clinical research and treatment.

Alternatively, phase changes may be important in understanding the relationship between PTSD symptoms and thyroid measures. Our clinical observations suggest that many patients with combat-related PTSD experience stages or phases of illness in which their impairments and symptoms are more or less prominent. Consideration of the potential significance of phase changes points to the possibility that the high thyroid/high hyperarousal association may be related to a specific phase in PTSD. Carefully designed longitudinal studies are needed to identify and explore more fully the phases in PTSD and to look for possible associations between phases and biological measures.

Although our study sample ($N = 65$) is reasonably large, it should be emphasized that our present results should be regarded as preliminary and in need of replication in additional PTSD patient samples, especially those studied under different conditions with regard to such factors as recruitment or selection, inpatient-outpatient status, group versus individual setting, ward milieu, style and intensity of treatment approach, type of trauma, and gender. In addition, the use of intensive longitudinal psychoendocrine studies of individual patients with PTSD to determine whether thyroid hormone levels covary with phase changes in PTSD symptoms would be especially helpful, not only in establishing the consistency of the present findings, but also perhaps in clarifying the direction of the relationships by means of a finely tuned study of the time course of the hormonal versus the clinical phase changes. Are episodic hyperarousal elevations, for example, generally associated with total and free T3 elevations; if so, does the clinical change precede or follow the hormonal change? Such studies, incidentally, could also provide much-needed knowledge about the time course of changes in different hormonal systems such as, for example, the thyroid and catecholamine systems, which may well have especially important interrelationships in PTSD (2).

The clinical significance of thyroid alterations in patients with combat-related PTSD is not clear. In this sample, the most significant relationship was found between CAPS-2 hyperarousal scores and TT3, which might indicate a high thyroid/high hyperarousal PTSD subtype or, alternatively, might suggest a high thyroid/high hyperarousal phase in the course of PTSD. In addition to the need for replication of the present findings, longitudinal studies are necessary to investigate the relationships between hormonal and clinical changes in patients with PTSD over time.

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